DoD Influenza Surveillance and Vaccine Effectiveness

Armed Forces Health Surveillance Center (AFHSC)
Naval Health Research Center (NHRC)
United States Air Force School of Aerospace Medicine (USAFSAM)
DoD Global Influenza Network Partners

Presentation to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) - 28 February 2014

CAPT Michael Cooper, PhD**
****Representing the DoD CONUS and OCONUS lab-based influenza surveillance activities**

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Briefing Outline

PURPOSE: Provide a concise update to the VRBPAC on DoD influenza surveillance activities, 2013-2014

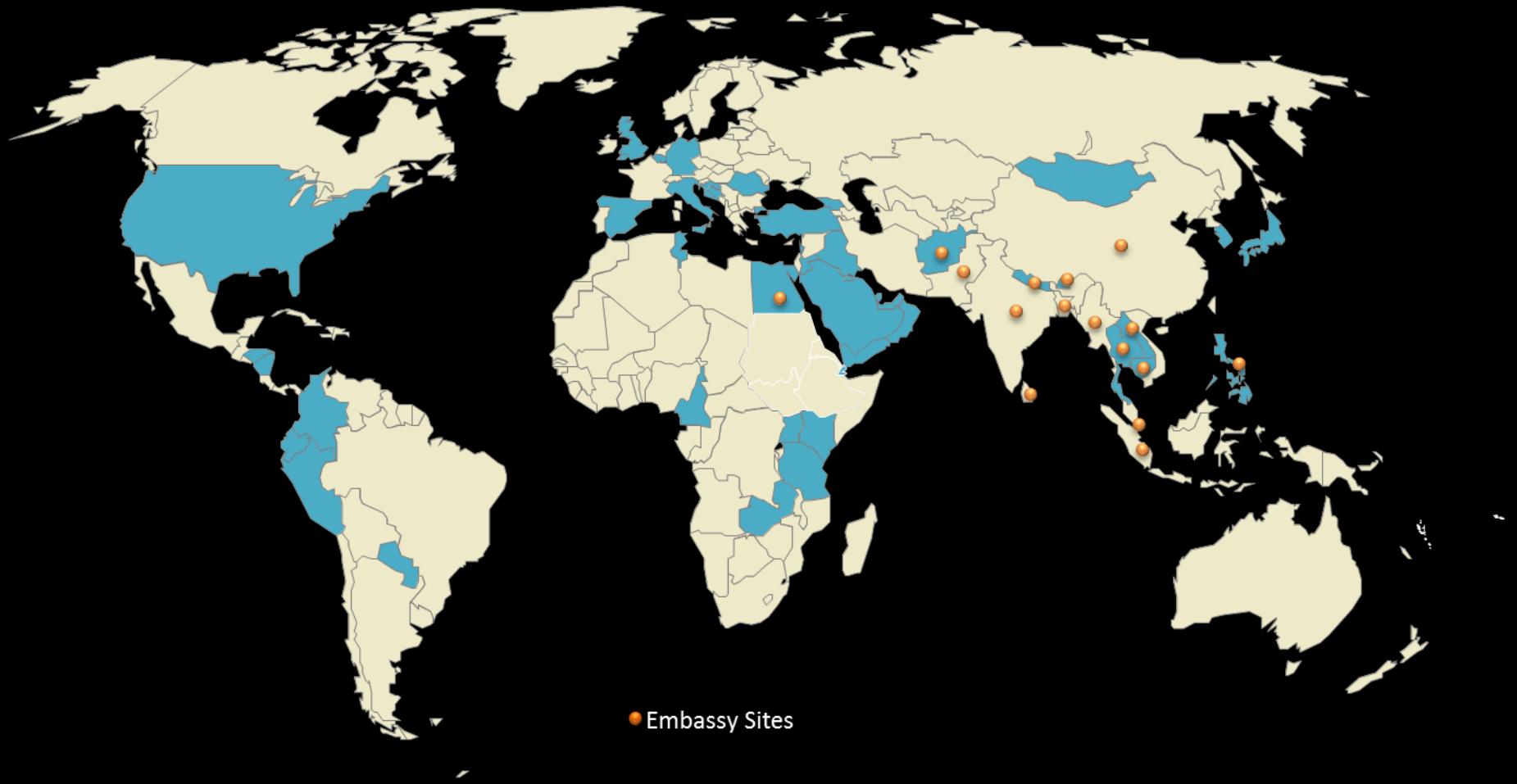
1. Strain Circulation
2. Molecular Analyses
3. Vaccine Effectiveness

Breadth of DoD Influenza Surveillance

- **Global Virus Surveillance**
  - Approximately 400 locations in over 30 countries
    - Military; Local government/academic
  - Extensive characterization capabilities within the DoD
    - Culture, HAI, PCR (battery), Sequencing, Serology (HI, MN)
  - Rapid sharing of results with CDC and/or regional WHO reference centers
    - ~30,000 samples collected and analyzed in fiscal year 2013
    - ~540 sequences submitted to GenBank in fiscal year 2013
- **Comprehensive Epidemiology and Analysis Capabilities**
  - 1.4 Million Active Duty records (health care utilization, immunizations, deployment, reportable diseases, etc)
    - Medical Surveillance Monthly Reports, Ad-hoc requests, Studies/analyses, Routine reports/summaries
    - Weekly influenza reports
    - Vaccine safety and effectiveness studies

GEIS-Supported Influenza Surveillance

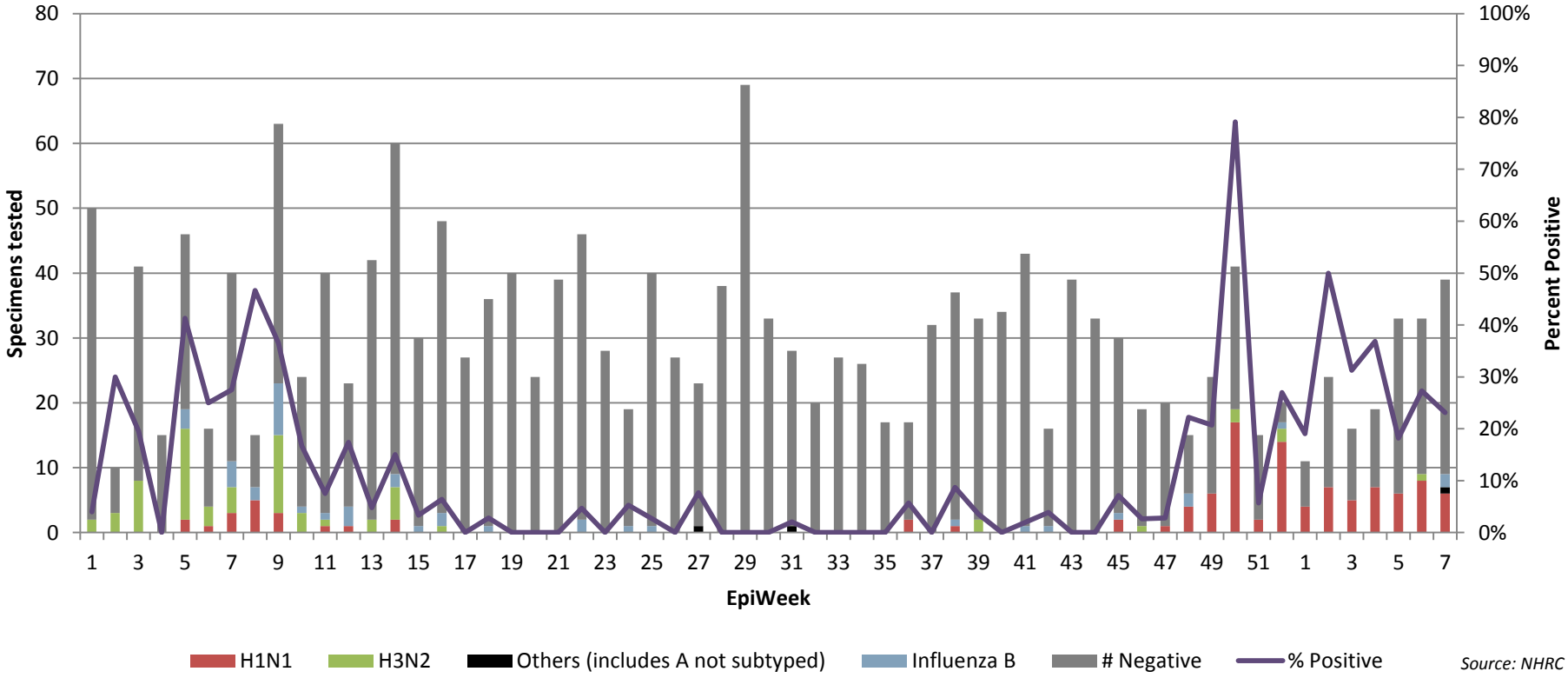
Footprint



In 2014:
--Over 30 countries
--Over 400 sites

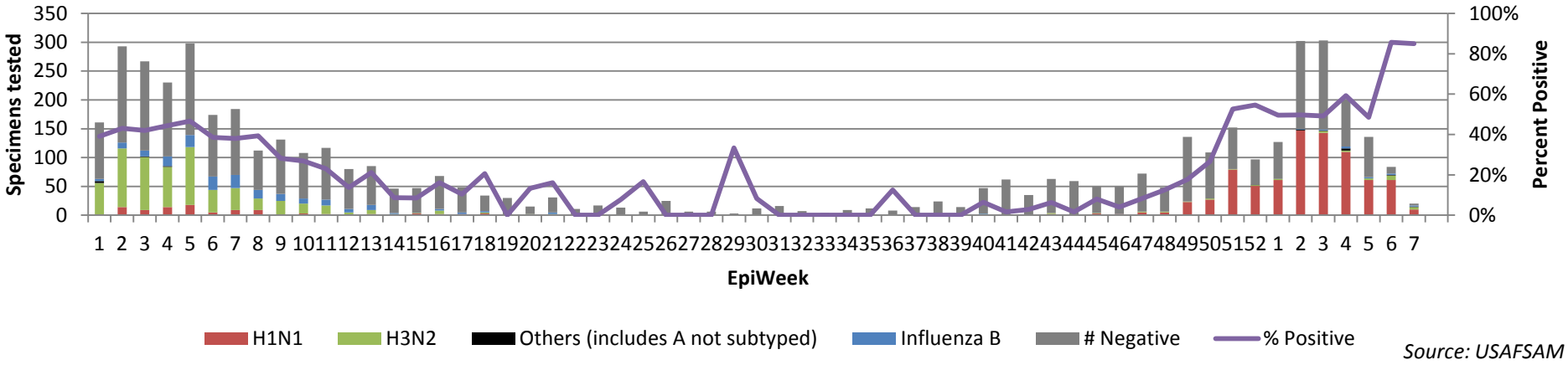
Strain Circulation

Military Recruits
North America
Number and Proportion of Specimens Positive for Influenza by Subtype
Week 1, 2013 - Week 7, 2014 (Feb 15, 2014)



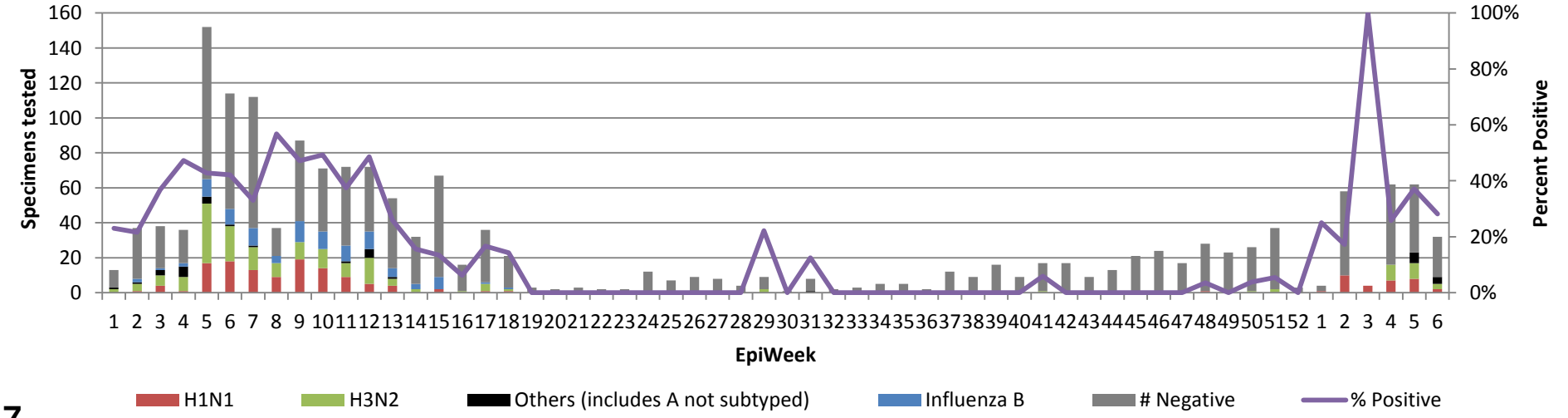
Source: NHRC

North America
Number and Proportion of Specimens Positive for Influenza by Subtype
Week 1, 2013 - Week 7, 2014 (Feb 15, 2014)



Source: USAFSAM

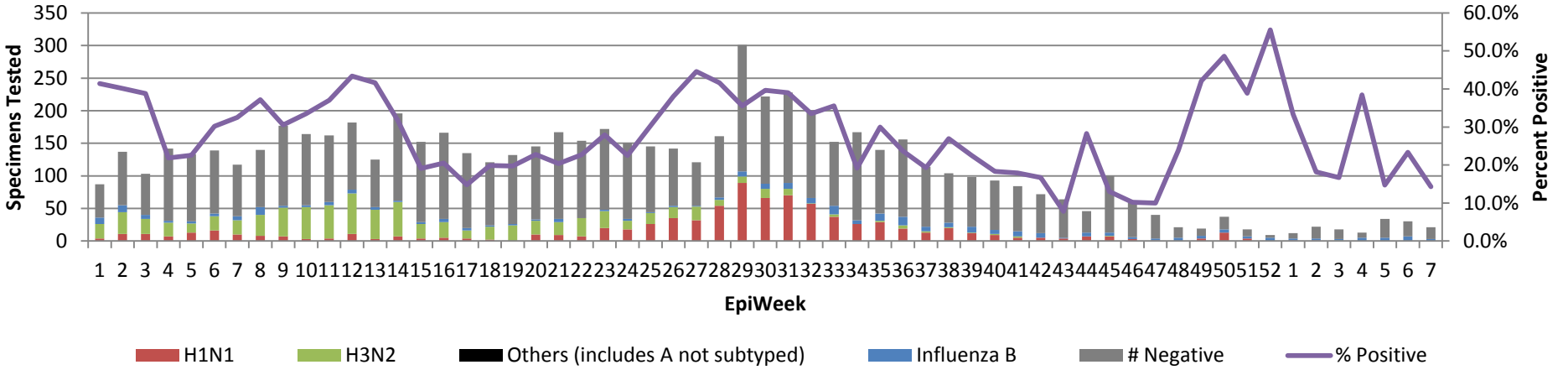
Europe
Number and Proportion of Specimens Positive for Influenza by Subtype
Week 1, 2013 - Week 7, 2014 (Feb 15, 2014)



Source: LRMC/PHCR-Europe

Latin America

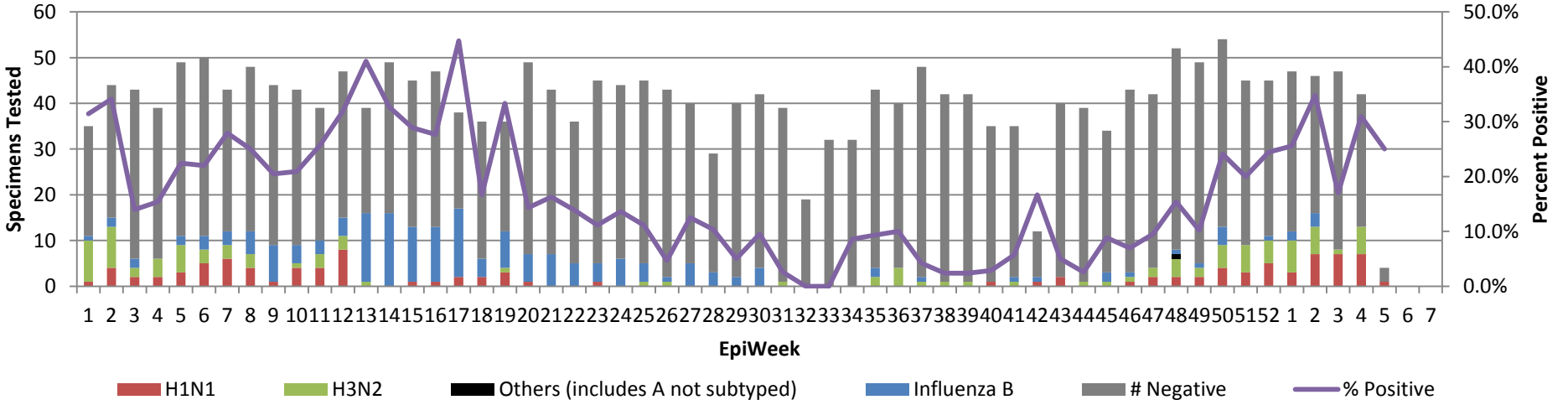
Number and Proportion of Specimens Positive for Influenza by Subtype
Week 1, 2013 - Week 7, 2014 (Feb 15, 2014)



Source: NAMRU-6

North Africa (Egypt)

Number and Proportion of Specimens Positive for Influenza by Subtype
Week 1, 2013 - Week 7, 2014 (Feb 15, 2014)

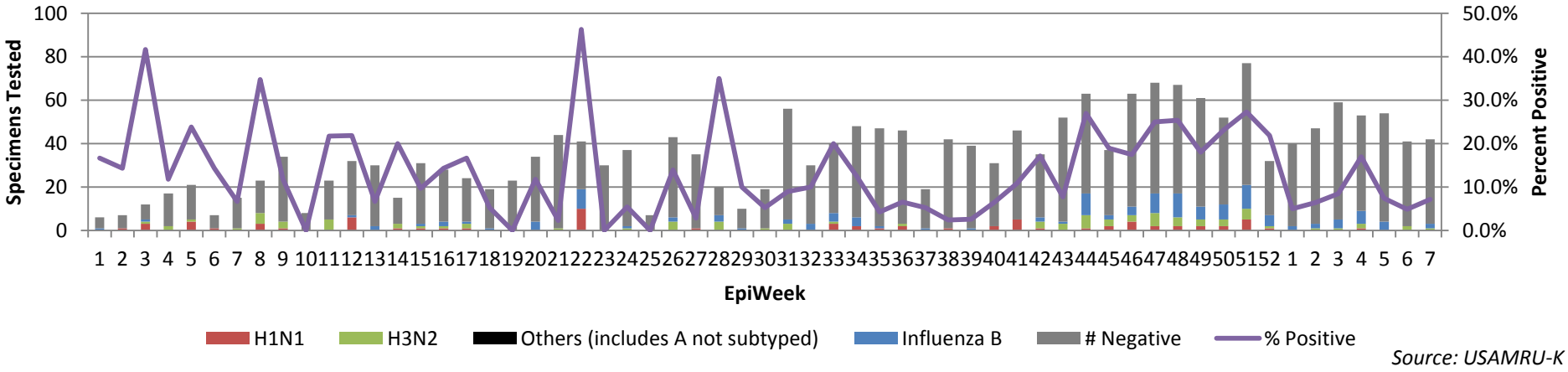


Source: NAMRU-3

Central and East Africa

Number and Proportion of Specimens Positive for Influenza by Subtype

Week 1, 2013 - Week 7, 2014 (Feb 15, 2014)

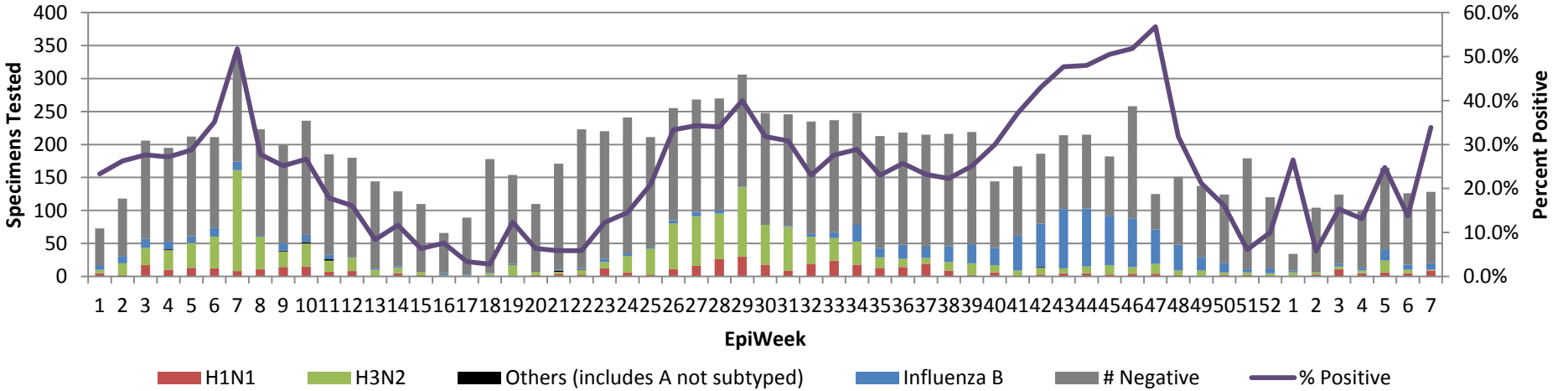


Source: USAMRU-K

East Asia

Number and Proportion of Specimens Positive for Influenza by Subtype

Week 1, 2013 - Week 7, 2014 (February 15, 2014)

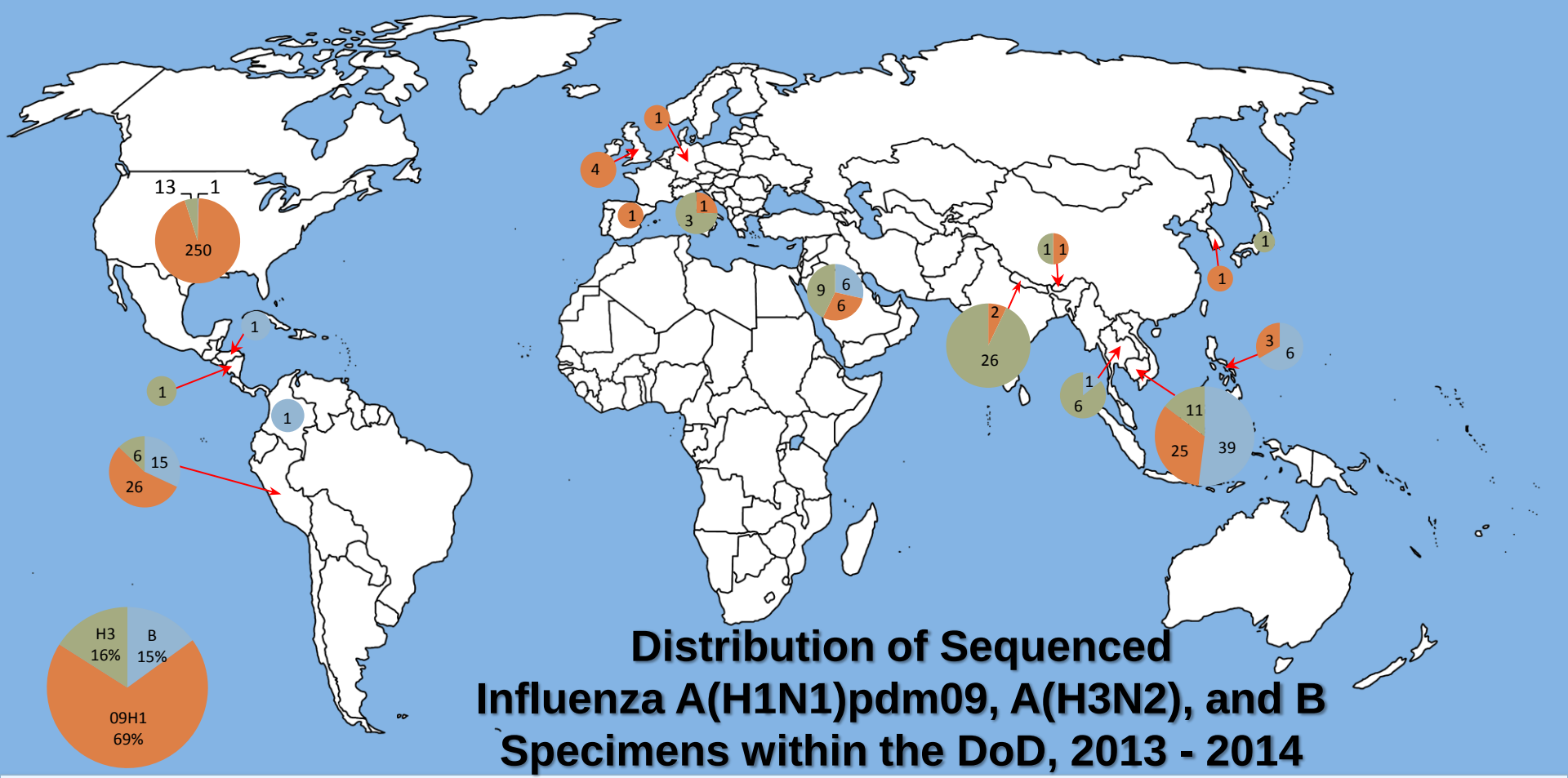


Source: AFRIMS, NAMRU-2, 65th Med Brigade

Summary of Circulating Strain Activity to date

- In North America, military members and dependents have experienced moderate to low flu activity; mostly H1N1 (>90% of positive samples were H1)
- Globally, influenza activity has been low in recent weeks especially in tropical regions.
  - Overall : Mix of H1N1, H3N2 and B
  - Influenza A peaked in East Asia (H3) and Latin America (H1) during the summer months
- Recruits & Shipboard: activity has been low, primarily flu A/H1N1

PHYLOGENETIC ANALYSIS



Distribution of Sequenced Influenza A(H1N1)pdm09, A(H3N2), and B Specimens within the DoD, 2013 - 2014

468 Total Sequences

Bhutan	Country 5	Korea	Spain
Cambodia	Germany	Nepal	Thailand
Columbia	Honduras	Nicaragua	United Kingdom
Country 1	Italy	Peru	United States
Country 2	Japan	Philippines	

Contributors

Armed Forces Research Institute of Medical Science – Bangkok, Thailand
Brooke Army Medical Center – San Antonio, Texas
Deployed Laboratories
Landstuhl Regional Medical Center – Rheinland-Pfalz, Germany
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USAF School of Aerospace Medicine – Wright-Patterson AFB, Ohio
Tripler Army Medical Center – Honolulu, Hawaii
Walter Reid Army Institute of Research – Silver Spring, Maryland

United States Air Force School of Aerospace Medicine
Public Health Epidemiology Laboratory
2510 5th Street, Wright-Patterson AFB OH 45433

Summary of Phylogenetic Analysis for A(H1N1)pdm09 HA 2013-2014

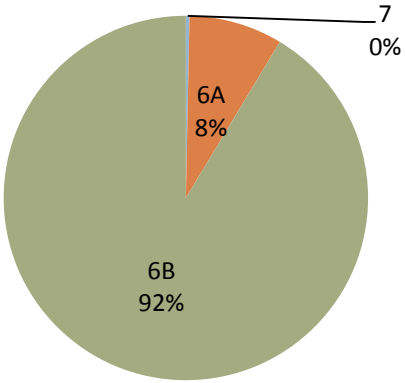
- Dominant subtype
- Due to size constraints, a representative analysis is displayed in the tree
- Similar to CDC analyses, the vast majority of sequences characterize into group 6B
- 92% of A(H1N1)pdm09 sequences possess changes at 163 and 256 (this distinguishes group 6B)
- Only one US sequence groups outside of 6B

Influenza A(H1N1)pdm09 HA Phylogenetic Analysis 2013-2014

- A(H1N1)pdm09 was predominant subtype this season. Accordingly, a larger number of A(H1N1)pdm09 strains were sequenced.
- The HA gene of A(H1N1)pdm09 demonstrates that the vast majority (92%) of circulating viruses belong to subgroup 6B; possessing K163Q and A256T changes.
- Due to larger numbers and limited space, not all specimens are included in the phylogenetic tree. Specimens were selected to provide a condensed representation of the strains sequenced.

N=321
A(H1N1)pdm09 Vaccine strain:
A/California/07/2009
Reference Strain
July-August 2013 17%
September-October 2013 3%
November-December 57%
January-February 23%
add gly Create Glycosylation Motif
loss gly Loss of Glycosylation Motif
F CDC Reference Strain
e Egg Isolate
LR Low Reactor to : A/California/07/2009 (≥8 fold)

HA Genetic Groups



Summary of Phylogenetic Analysis for A(H3N2) HA 2013-2014

- Small number of specimens, most came from tropical or southern hemisphere June to Sept
- All influenza H3 sequences characterize into group 3C. Previous years' groups 5 and 6 have not been found in DoD surveillance to date.
- All H3 sequences possess a change at 145 and 70% possess two changes that characterize into subgroup 3C.3. This is a continuation of the direction from 2012-2013 season.
- Only 15% of H3 sequences were from US

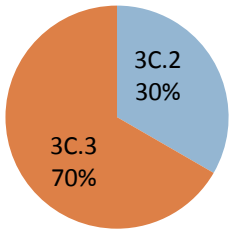
Influenza A(H3N2) HA Phylogenetic Analysis 2013-2014

- Low numbers of H3N2 collected and sequenced from November 2013 to present. Also very few U.S. samples.

- The HA gene of H3N2 demonstrates that a majority (70%) of recently sequenced viruses belong to subgroup 3C.3 and share the following changes: T128A (loss of potential glycosylation site) and R142G.

- The other sequenced viruses (30%) characterize into group 3C.2 sharing a change at D489N.

HA Genetic Groups



N=77
A/H3N2 Vaccine strain: A/Texas/50/2012
Reference Strain
July-August 2013 53%
September-October 2013 16%
November-December 18%
January-February 13%
add gly Create Glycosylation Motif
loss gly Loss of Glycosylation Motif
F CDC Reference Strain
e Egg Isolate
LR Low Reactor to : A/Texas/50/2012 (≥8 fold)

Summary of Phylogenetic Analysis for B HA 2013-2014

Yamagata

- Overall in our network, 86% of our Bs were Yamagata
- Most characterize into group 2 with B Yamagata vaccine
- 37% reverted to group 3, like 2012-2013 vaccine, B/Wisconsin/1/2010, including a single US sequence and several sequences from deployed locations

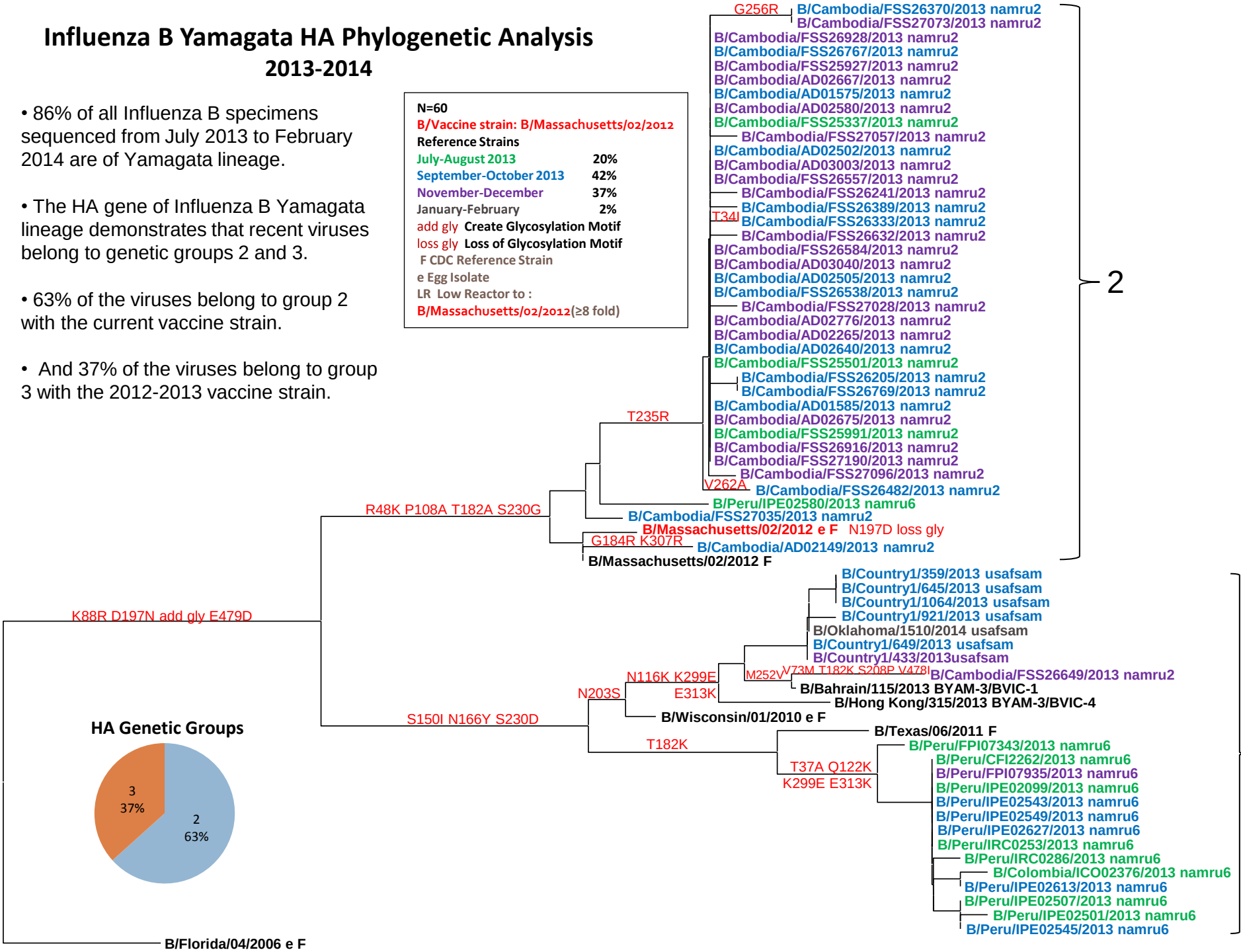
Victoria

- Very small numbers (10 sequences) all from outside US; collected from July through August
- All specimens sequenced similarly to the dominant group from the previous season (group 1A)

Influenza B Yamagata HA Phylogenetic Analysis
2013-2014

- 86% of all Influenza B specimens sequenced from July 2013 to February 2014 are of Yamagata lineage.
- The HA gene of Influenza B Yamagata lineage demonstrates that recent viruses belong to genetic groups 2 and 3.
- 63% of the viruses belong to group 2 with the current vaccine strain.
- And 37% of the viruses belong to group 3 with the 2012-2013 vaccine strain.

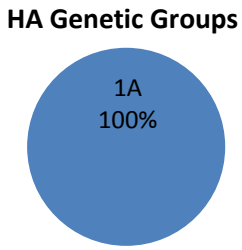
N=60
B/Vaccine strain: B/Massachusetts/02/2012
Reference Strains
July-August 2013 20%
September-October 2013 42%
November-December 37%
January-February 2%
add gly Create Glycosylation Motif
loss gly Loss of Glycosylation Motif
F CDC Reference Strain
e Egg Isolate
LR Low Reactor to :
B/Massachusetts/02/2012(≥8 fold)



Influenza B Victoria HA Phylogenetic Analysis
2013-2014

- Low numbers of viruses sequenced due to limited cases circulating in DoD populations.
- All Influenza B Victoria lineage sequences were collected in July and August 2013.
- All of the specimens collected came from areas that do not exhibit a northern hemisphere-like Influenza season.
- The HA gene of Influenza B Victoria lineage demonstrates recent viruses belong to genetic group 1A.
- Group 1A viruses share three amino acid changes at positions N75K, N165K and S172P of the HA gene similar to the vaccine recommendation.

N=10
B/Vaccine strain: B/Brisbane/60/2008
Reference Strains
July-August 2013 100%
September-October 2013 0%
November-December 2013 0%
January-February 2014 0%
add gly Create Glycosylation Motif
loss gly Loss of Glycosylation Motif
F CDC Reference Strain
e Egg Isolate
LR Low Reactor to : B/Brisbane/60/2008 (≥8 fold)



VACCINE EFFECTIVENESS (VE)

Preview

- Mid-year estimates provided by:
  - US Air Force School of Aerospace Medicine (USAFSAM),
  - Naval Health Research Center (NHRC)
  - Armed Forces Health Surveillance Center (AFHSC)
- Case-Control studies, logistic regression used to estimate VE
  - Two studies used control-test negative method, one study used health controls
  - No analyses by flu subtype (over 90% of flu samples were H1N1)

United States Air Force School of Aerospace Medicine (USAFSAM)

- Adjusted Estimates of Vaccine Effectiveness
  - Population: Service members and dependents (CONUS and OCONUS)
  - Separate analyses for service members & dependents
  - Analyses by vaccine type (LAIV & IIV)
  - No analyses by flu subtype (over 93% of flu samples were H1N1)
  - Models adjusted for age and collection period (4 quartiles)
  - Cases confirmed by RT-PCR, viral culture
    - Service members n=271, dependents n=339
  - Controls are test-negative for influenza
    - Service members n=485, dependents n=469
  - 56% of cases and 60% of controls were vaccinated

DoD Mid-Season Vaccine Effectiveness: 2013-2014

Crude and adjusted influenza vaccine effectiveness (VE) estimates, mid-season (September 29, 2013 - January 25, 2014)
USAFSAM's DoD Global, Laboratory-based, Influenza Surveillance Program

Beneficiary Status[a]	Vaccine Type	Cases	Controls	Crude OR	VE Crude %	Adjusted OR	VE Adjusted %
Dependents	Overall	339	469	0.56	43.86 (23.84, 58.62)	0.34	65.81 (50.91, 76.19)
	LAIV	234	248	0.95	5.45 (-54.42, 42.11)	0.60	39.77 (-5.29, 65.54)
	IIV	302	425	0.43	56.74 (37.92, 69.86)	0.26	73.58 (59.59, 82.73)
Service Members	Overall	271	485	3.32	-232 (-455.83, -97.78)	0.84	15.73 (-69.94, 58.21)
	LAIV	201	332	5.19	-419 (-840.41, -186.98)	1.19	-19.5 (-164.36, 46.01)
	IIV	83	243	2.24	-124 (-296.84, -26.20)	0.60	39.68 (-33.88, 72.83)

Note: OR = odds ratio; VE = vaccine effectiveness; LAIV =live, attenuated influenza vaccine (LAIV4); IIV = inactivated influenza vaccine (IIV3, IIV4, ccIIV3)

[a] Dependents include any individual treated at a military treatment facility that is not a service member (i.e. child, spouse, retiree, etc.). Service members include any active duty, guard, or reserve member from any service branch.

Notes:
1) For individuals <9 years of age, two vaccinations are recommended; for this study, this age group was handled the same as the older age groups with respect to vaccination (a subject was considered vaccinated if one influenza vaccination was received at least 14 days prior to specimen collection date).
2) Overall adjusted VE was calculated using multivariable logistic regression with adjustment for age and time period (collapsed into four equal quartiles).
3) All influenza subtypes (H1: n=569, H3: n=17, A/not subtyped: n=16, B: n=6) were included in this analysis. An H1 specific model is not presented due to the fact that H1 predominately (93.4%) drove this analysis and H1 specific VE results were very similar to those presented.
4) 341 (55.9%) cases (116 IIV, 223 LAIV, 2 unk) and 570 (59.8%) controls (284 IIV, 279 LAIV, 7 Unk) were vaccinated (n=911).

Naval Health Research Center (NHRC)

- Adjusted Estimates of Vaccine Effectiveness
  - Population: Civilians only
    - Dependents Southern California and Illinois
    - Civilians at clinics and hospitals near US-Mex border
  - Small numbers: no analyses on vaccine type
  - Adjusted for: age, location of treatment, hospitalization status
  - Cases: n=106; confirmed by RT-PCR or viral culture
  - Controls: n=278; test-negative
  - Vaccination Rates: cases 19%, controls 33%
  - Overall, adjusted VE was 53%; 65% for pH1N1; both sig at 0.05

NHRC- Vaccine Effectiveness (VE)

- 409 ILI cases enrolled between 11/25/13 and 1/16/2014
  - 384 with known vaccination status
  - Lab-confirmed influenza by CDC RT-PCR assay
  - VE = 1 – Odds ratio

Vaccine Effectiveness Estimates				
	Cases	Controls	VE (crude)	VE (adjusted)
Overall	106	278	52 (17, 72)	53 (17, 74)*
pH1N1	84	278	59 (23, 78)	65 (33, 81)**

*Adjusted for hospitalization status (inpatient/outpatient), age, and study population (San Diego, Illinois, US-Mex border)
**Adjusted for hospitalization status (inpatient/outpatient), and age

AFHSC

- Matched Case Healthy-Control Study of VE
  - Population: Active component service members
    - Army, Navy, Air Force, Marines, Coast Guard
    - CONUS and OCONUS
  - Lab-confirmed flu cases (n=575)
    - Rapid, RT-PCR, or culture
  - Healthy Controls (n=2267)
    - Medical encounter for musculoskeletal or mental health condition with no respiratory conditions reported
    - No medical encounters for influenza during season
    - Matched to cases by sex, age, date of encounter (+/- 3 days), and location
  - Models adjusted for 5-yr vaccination status (Y/N)
  - Overall and vaccine-type VE calculated

AFHSC Mid-Season 2013-2014 Matched Case-Healthy Control VE Study (Active Component)

- 90% of cases were vaccinated; 91% of controls
- 94% had prior flu vaccination in previous 5 years
- Adjusted VE of 28 for those who received IIV (not significant)
- Adjusted VE for those who received LAIV was -17; not statistically significant

AFHSC Mid-Season 2013-2014 VE Estimates Active Component

Vaccine Type	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*	Vaccine Effectiveness (95% CI)
Overall	518 (90)	2060 (91)	0.89 (0.63,1.27)	0.93 (0.65,1.32)	7 (-32,35)
LAIV	324 (56)	1086 (48)	1.13 (0.78,1.63)	1.17 (0.81,1.70)	-17 (-70,19)
IIV	183 (32)	910 (40)	0.69 (0.47,1.00)	0.72 (0.49,1.05)	28 (- 5,51)
Unvaccinated	57 (10)	207 (9)	Ref	Ref	Ref

Notes:

1. OR = Odds Ratio
2. IIV = inactivated influenza vaccine
3. LAIV = live, attenuated influenza vaccine
4. *Adjusted for vaccination status in 5 years prior
5. ** Includes recombinant and unspecified vaccination types

Summary of Results

- VE for civilians was significant and relatively high for those vaccinated with IIV
- For military members VE was not statistically significant

Limitations

- Generalizability
  - Subjects were sick enough to seek medical attention, can't comment on vaccine impact for less severe cases
  - Active Duty mil pop is highly immunized, this could have a negative impact on VE (potential method issues and biological effects such as attenuated immune response with repeated exposures)
  - The military population is younger and healthier; cannot comment on vaccine impact in older, high-risk pops
  - Unable to compare flu subtypes
- Vaccination Data
  - Some vaccination data relied on patient recall

Summary

- The DoD maintains a robust surveillance system with capacity to assess mid-season and end-of-season VE and molecular characterization of circulating viruses
- Analysis of our network's specimens supports continued use of the current A/H1N1, A/H3N2, B Victoria and B Yamagata vaccine strains

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AFHSC

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CAPT Kevin Russell

AFRIMS

Dr. Ans Timmermans

Ms. Tippa Wongstitwilairoong

MAJ Stefan Fernandez

LTC Samuel Yingst

65th MEDICAL BRIGADE

CPT Mary Guyton

MAJ Matt Brown

MAJ Bryan Gnade

LRMC/PHCR-Europe

Ms. Michele Balihe

LTC Edward Ager

COL John Mitchell

NAMRU-2

Mr. Agus Rachmat

Mr. Yi Chenda

CAPT Patrick Blair

NAMRU-3

LCDR Gabriel Defang

Mr. Ehab Amir

Mr. Emad Maher

Mr. Emad M. Elassal

Ms. Caroline Fayez

Ms. Mary Younan

LT Cheryl Rozanski

NAMRU-6

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Capt Robel Yohannes

Dr. Elizabeth Macias

Ms. Linda Canas

Mr. James Hanson

Ms. Katie Tastad

Mr. James Smith

Mr. Benjamin Connors

Ms. Laurie DeMarcus

Ms. Samantha Jones

USAMRU-K

Dr. Wallace Bulimo

COL Rodney Coldren

Mr. Cyrille Djoko

Dr. Bernard Erima

Mr. Derrick Mimbe

Dr. Lucy Ndip

Mr. James Njiri

Dr. Karen Saylors

LTC Eyako Wurapa

WRAIR

Dr. Huo-Shu Houng

MAJ Richard Jarman

Questions

CAPT Michael Cooper, PhD
Head, Dept. of Respiratory Infections Surveillance
Tel: 301-319-3258
E-mail: Michael.j.Cooper119.mil@mail.mil

Col James Cummings
Director GEIS
E-mail: James.F.Cummings6.mil@mail.mil

CAPT Kevin L. Russell, MD, MTMH
Director, AFHSC
Tel: 301-319-3240
E-mail: Kevin.I.Russell14.mil@mail.mil

AFHSC Mid-Season 2013-2014 Matched Case-Health Control VE Study (Active Component)

Distribution by Select Factors	Cases n (%)	Controls n (%)
Overall	575 (100)	2267 (100)
Sex*		
M	458 (80)	1815 (80)
F	117 (20)	452 (20)
Age*		
18-24	133 (23)	522 (23)
25-29	109 (19)	427 (19)
30-39	224 (39)	890 (39)
40+	109 (19)	428 (19)
Service		
Army	217 (38)	914 (40)
Navy	85 (15)	299 (13)
Air Force	231 (40)	876 (39)
Marine Corps	35 (6)	149 (7)
Coast Guard	7 (1)	29 (1)

Note: *Controls matched to cases on these factors; Controls also matched on date of encounter and location (distribution shown on next slide)

AFHSC Mid-Season 2013-2014 Matched Case-Health Control VE Study (Active Component)

Distribution by Select Factors	Cases n (%)	Controls n (%)
Overall	575 (100)	2267 (100)
Location of Diagnosis*		
US	504 (88)	1990 (88)
Non-US	71 (12)	277 (12)
Month of Diagnosis*		
September	8 (1)	29 (1)
October	10 (2)	43 (2)
November	18 (3)	67 (3)
December	186 (32)	698 (31)
January	320 (56)	1316 (58)
February**	33 (6)	114 (5)
Flu Vaccination in Prior 5 years***		
No	51 (9)	129 (6)
Yes	524 (91)	2138 (94)

Note: *Controls matched to cases on these factors (at finer granularity); Controls also matched on sex, age(distribution shown on previous slide)

** Partial Month of data

*** Regression Model adjusted for this factor

Active Component Distribution of Immunization Types by Service – 2013-2014 Midseason

Vaccine Type	Army	Navy	Air Force	Marines	Coast Guard
LAIV	31%	34%	50%	43%	49%
IIV	59%	64%	39%	55%	45%
Other**	10%	2%	11%	2%	6%

Notes:

1. LAIV = live, attenuated influenza vaccine
2. IIV = inactivated influenza vaccine
3. ** Includes recombinant and unspecified vaccination types

Collect 2 Swabs from Each Pt with "Influenza-Like Illness" (ILI)

Follow DoD case definition for ILI:

- **FEVER** ≥100.5°F (38°C)

  plus

- **COUGH**

  &/or

- **SORE THROAT**
  - Symptom onset within 72 hours of presentation

Collect 2 swabs, 1 from each nostril